Total Synthesis of TAN-1057 A/B, a New Dipeptide Antibiotic from *Flexibacter* sp. PK-74☆

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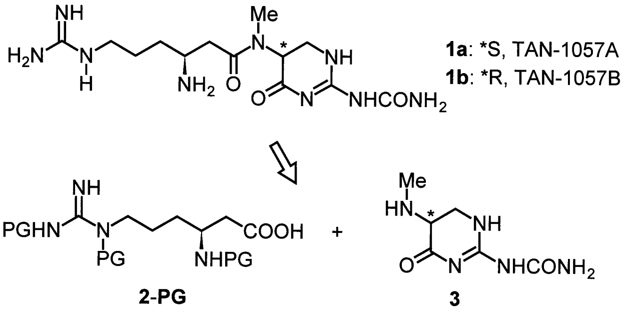
TAN-1057 (**1a**, **b**) – a new natural dipeptide antibiotic active against methicillin resistant strains of *Staphylococcus aureus* – was synthesized starting from N^{α},N^{δ},N^{ω}-tri-Z-L-arginine **20b** via the corresponding diazoketone **21b**. This upon photolysis rearranged to the ketene which was trapped by (±)-2,4,5,6-tetrahydro-5-methylamino-2-ureidopyrimidin-4-one (**3**) to yield the fully protected dipeptide **23** (30%). The latter was deprotected by hydrogenolysis to give the final compound as a mixture of two epimers – TAN-1057A, B – isolated previously from a strain of *Flexibacter* sp. PK-74. The intermediate **3** was prepared from 3-amino-2-(*N*-Z-*N*-methylamino)propionic acid methyl ester hydrochloride (**16**) and 2-methyl-2-thiopseudobiuret hydroiodide (**18**) in one step in 35% yield.

Several strains of staphylococci, streptococci, enterococci, and other bacteria which have developed a resistance against β-lactames, macrolides, and tetracyclines are causing an ever increasing problem in antibiotic therapy. The search for new antibiotics with completely different mechanisms of action is therefore an urgent worldwide activity, even though the battle may never end. A few years ago, Japanese scientists have isolated from a strain of *Flexibacter* sp. PK-74, a new compound which showed remarkably strong antibacterial activity against methicillin resistant strains of *Staphylococcus aureus* (MRSA)[1]. The structure elucidation of this compound which was termed TAN-1057 A/B, revealed that it was a mixture of the two epimeric dipeptides **1a** and **1b**. The heterocyclic moiety in **1a**,**b** is related to 2,3-diaminopropionic acid, the β-amino acid side chain is (*S*)-β-homoarginine which has recently been synthesized[2]. We embarked on a total synthesis of **1a**, **b** two years ago before any activities by other groups had been reported[3][4].

TAN-1057 A/B is soluble in water, but rather sensitive towards hydrolysis and therefore slowly looses its antibacterial activity in aqueous solution. Hydrolysis causes an irreversible opening of the six-membered heterocycle at the CO–N bond, and this process is catalyzed by acids. Strong bases can also cause hydrolytic cleavage especially of the carbamoylacylguanidine fragment in the molecule.

The most straightforward strategy for the synthesis of TAN-1057 A/B would be based on an amide coupling of an appropriately protected (*S*)-β-homoarginine **2** with the tetrahydropyrimidinone derivative **3** followed by removal of the protecting groups (PG). Several approaches to the heterocycle **3** were tried. The first attempt was stimulated by the known cyclization of *N*-(*tert*-butoxycarbonyl)-*O*-tosyl-L-serine methyl ester (**7**) with hydrazine giving 4-(*tert*-butoxycarbonylamino)pyrazolidin-3-one[5]. If compound **7** would react with *N*-carbamoylguanidine in an analogous way, the six-membered ring closure would yield the desired compound **3-Boc** with a *tert*-butoxycarbonyl protecting group at the exocyclic nitrogen atom. Compound **7** was synthesized starting from *N*-methyl-L-serine (**4**)[6], and its reactivity towards *N*-carbamoylguanidine was tested (Scheme 2).

Scheme 1



Unfortunately, only dehydrotosylation occurred to yield the known *N*-(*tert*-butoxycarbonyl)-*N*-methyldehydroalanine methyl ester (**8**)[7]. This compound **8**, however, appeared to be a potential starting material for another approach to the heterocycle **3** via compound **9** which should be formed from **8** and guanidine by Michael addition and subsequent

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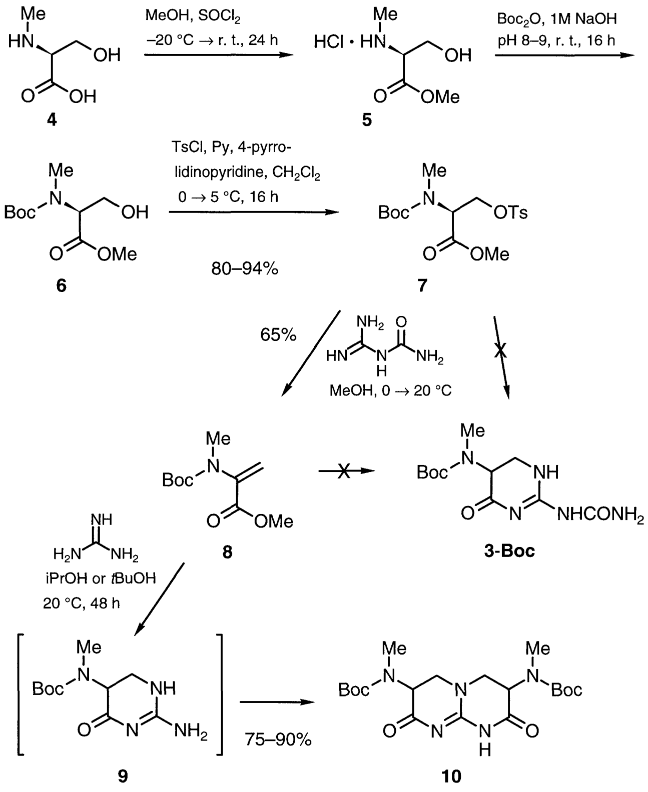
cyclization analogous to the known method for the preparation of 2-amino-5,6-dihydro-4(1*H*)-pyrimidinones[8]. However, the reaction of **8** with guanidine proceeded all the way to the bicyclic compound **10** by Michael addition of the intermediate compound **9** to a second molecule of **8** and subsequent cyclization. This interesting domino reaction to yield **10** (up to 85% isolated) occurred even with slow addition of **8** to guanidine (over 36 h at 40°C).

Scheme 2



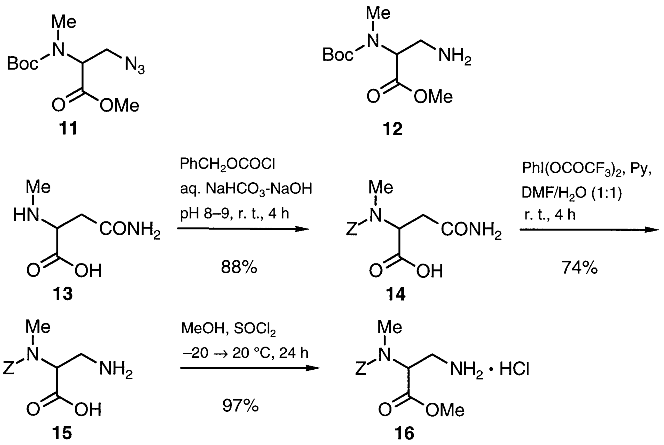
According to these results it appeared to be necessary to bring the β-amino group in with the α-amino acid fragment before performing the ring closure to the heterocycle **3**. This should be achieved by condensation of an appropriate 2,3-diaminopropionic acid derivative (e.g. **12**) with a reagent providing the *N*-carbamoylamidino function followed by cyclization.

The synthesis of methyl 3-amino-2-(*N*-Boc-*N*-methylamino)propionate (**12**) might be attempted through a Mitsunobu reaction of the ester **6** with HN_3 and subsequent reduction of the azido group. Unfortunately, treatment of **6** with a 0.8 M solution of hydroazotic acid in benzene, triphenylphosphane, and diethyl azodicarboxylate (DEAD) in THF gave an unseparable mixture of the azido ester **11** and the dehydroalanine derivative **8** in a ratio of ca. 2:3. The low yield of the azido ester **11** (35%) could not be improved by using an excess of the reagents.

Another possible route to the important intermediate **15**, though racemic, starts from the known N^{α}-methyl-DL-asparagine (**13**)[9] (Scheme 3).

Therefore N^{α}-methyl-DL-asparagine (**13**) was protected by reaction with benzyl chloroformate (ZCl) to give the compound **14**. The Z-protecting group was preferred at this stage as it can be cleaved hydrogenolytically, while the Boc-deprotection requires strongly acidic conditions and the six-membered ring in TAN-1057 (and probably its precursors) is sensitive towards acidic hydrolysis.

Scheme 3

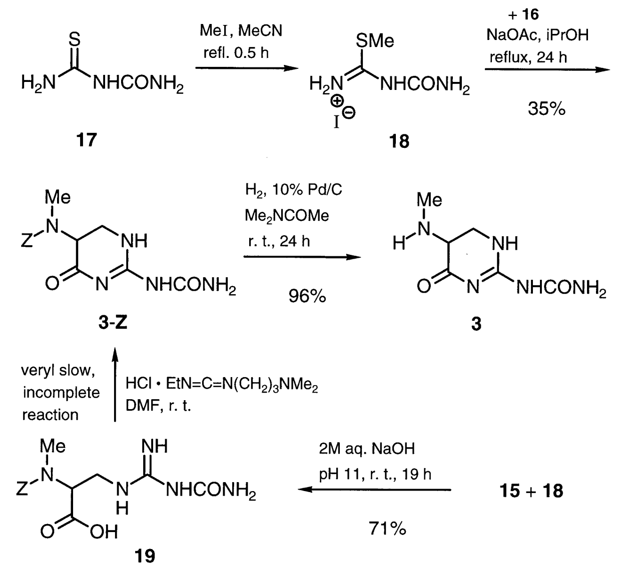


Oxidation of the amide nitrogen in **14** by iodobenzene bis(trifluoroacetate) as described for a similar compound[10] was accompanied by Hoffmann degradation and gave the required N^{α}-benzyloxycarbonyl-N^{α}-methyl-2,3-diaminopropionic acid (**15**) which was esterified according to the standard protocol[11], to yield amino acid **16** as the first key intermediate.

The isothiuronium salt **18**, chosen as a reagent to introduce the *N*-carbamoylamidino function, was obtained from monothiobiuret (**17**) (Scheme 4) as described earlier[12][13]. Although there was no information in the literature on reactions of **18** with amines to form carbamoylguanidines, a very similar "thiocarbamoylguanidination" of amines with the thioanalog of **18** was described recently[14]. Various bases and solvents were tested in order to direct the coupling reaction between the salt **18** and ester **16** towards the required product **3-Z**, but even under optimized conditions the yield was only moderate (35%).

The solubility of the heterocyclic compound **3-Z** is low, and it precipitates directly from the reaction mixture making the isolation and purification easy. When the amino acid **15** was treated with the salt **18** in the presence of 2 M aqueous sodium hydroxide, the open-chain acid **19** was formed in good yield, but again, due to low solubility, the final ring-closure to **3-Z** proceeded very slowly and incompletely only in DMF suspension with the water-soluble *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride as a condensing reagent, 50% of the acyclic **19** was recovered after 3 d in a 1:1 mixture with **3-Z**. The heterocycle **3-Z** is practically not soluble in methanol, better soluble in DMSO, acetic acid, DMA, and other amide solvents like DMF or *N*-methylpyrrolidone. Therefore, the attemted hydrogenolytic deprotection of **3-Z** was not observed in methanol, it was accompanied with ring-opening in glacial acetic acid, and only in dimethylacetamide the removal of the Z-protecting group proceeded smoothly allowing the isolation

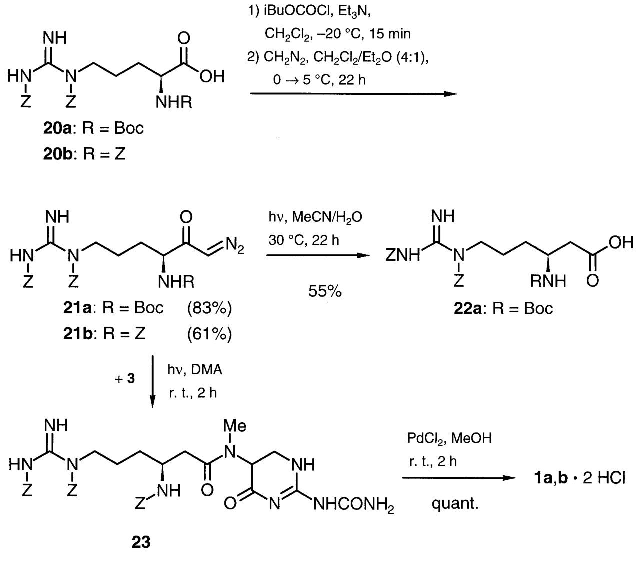
Scheme 4



of the deprotected heterocycle **3** in nearly quantitative yield.

The last prerequisite to complete the synthesis of TAN-1057 was the connection of the homoarginine residue **2** (PG = Z, Scheme 1) to the heterocycle **3**. Towards this goal, the tris-Z-protected diazoketone **21b** – precursor to the compound **2** (PG = Z) – was synthesized by a procedure closely analogous to the one reported for the bis-Z-mono-Boc-protected compound **21a**[2], starting from the $N^{\alpha},N^{\delta},N^{\omega}$-tri-Z-L-arginine derivative **20b** instead of N^{α}-Boc-N^{δ},N^{ω}-bis-Z-L-arginine **20a**.

Scheme 5



While the photolysis of **21a** in moist acetonitrile leads to the *N*-protected homoarginine **22a** itself, the ketene formed from **21a** upon photolysis in anhydrous acetonitrile could also be trapped by α-aminoesters to form dipeptide esters directly[2]. This trapping offers itself as a method of linking the homoarginine **2** (PG = Z) to the tetrahydropyrimidinone derivative **3**.

Thus, the Wolff-rearrangement of **21b** in the presence of **3** was employed as a key step in the synthesis of TAN-1057 A/B to give the tris-Z-derivative **23** right away.

Because of the insufficient solubility of the heterocycle **3** in acetonitrile, the solvent recommended for an analogous peptide coupling[2], the photolysis of **21b** in the presence of **3** was run in dimethylacetamide in which a rapid reaction was observed, and the coupling product **23** could be isolated with satisfactory yield (30%). Chromatographic purification of **23** on silica gel was not possible due to its instability, but the compound could be purified by recrystallization from dichloromethane.

Hydrogenolytic deprotection of **23** to **1a**,**b** was achieved in methanol in the presence $PdCl_2$ in nearly quantitative yield. The bishydrochloride **1a**,**b** was isolated as a mixture of two epimers (1:1) with ≥95% chemical purity. The ^{1}H- and ^{13}C-NMR spectra of this product corresponded to the literature data[1][4]. Deviations up to ±0.4 ppm for the broad signals attributed to C-2, C-4, and the ureido carbons are certainly due to the prototropy in the *N*-acyl-*N'*-carbamoylguanidine fragment.

The procedure allowed the preparation of gram quantities of TAN-1057 A/B. The thus available amounts of synthetic TAN-1057 A/B are sufficient for further experiments towards the separation and tedious purification of the easily epimerizing (cf. ref.[4]) diastereomers A and B, as well as a detailed study of its biological activity which are in progress.

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Experimental Section

Melting points (uncorrected) were determined in capillaries using the apparatus produced by Büchi. – FT-IR: Bruker IFS 66. – ^{1}H NMR: Bruker AM 250 (250 MHz), δ = 0 for tetramethylsilane, 2.49 for [D$_5$]DMSO, 3.50 for HDO and 7.26 for $CHCl_3$. Characteristics of splitting due to spin-spin coupling: s = singlet (br. s = broad singlet), d = doublet, t = triplet, q = quartet, m = multiplet, m_c = centrosymmetrical multiplet; * = assignment is not unequivocal. – ^{13}C NMR: Bruker AM 250 (62.9 MHz), δ = 39.5 for [D$_6$]DMSO, 77.0 for $CDCl_3$. The DEPT-135 pulse sequence was used for the determination of signal types: + = primary or tertiary carbon (positive DEPT-signal), – = secondary carbon (negative DEPT-signal), C_{quat} = quaternary carbon (no visible DEPT-signal). – MS (EI) and MS (HR-EI): Finnigan MAT 95 and Varian CH 5 spectrometers at 70 eV. MS (HR-EI): preselected ion peak matching at R >> 10000 to be within ±2 ppm of the exact masses. – Preparative column chromatography was performed on Merck silica 60 (0.063–0.200 mm) with distilled solvents. – Analytical thin-layer chromatography (TLC): Macherey-Nagel ready-to-use plates Alugram Sil G/UV$_{254}$. Detection under a UV-lamp at 254 nm, development with molybdatophophoric acid solution (5% in ethanol) or ninhydrin solution in butanol/glacial acetic acid mixture. – Elemental analysis: Microanalytical Laboratory of the Institut für Organische Chemie der Universität Göttingen. – Solvents were dried according to commonly used procedures.

N-Methyl-L-serine Methyl Ester Hydrochloride (**5**)[15]: From *N*-methyl-L-serine **4**[6] (3.99 g, 33.4 mmol) was obtained 4.59 g (81%)

of **5**, m. p. 137−139°C. − ^{1}H NMR ($CDCl_3$+[D_6]DMSO): δ = 2.80 (br. s, 3 H, CH_3N), 3.82 (s, 3 H, CH_3O), 3.95−4.15 (m, 3 H), 9.5 (br. s, NH_2). − ^{13}C NMR ($CDCl_3$+[D_6]DMSO): δ = 29.73 (+, CH_3N), 51.10 (+, CH_3O), 56.47 (−, CH_2O), 60.20 (+, CH), 165.96 (C_{quat}, CO). − $C_5H_{11}NO_3 \cdot HCl$ (169.6): calcd. C 35.41, H 7.13, N 8.26; found C 35.30, H 7.25, N 8.16.

*N-tert-Butoxycarbonyl-N-methyl-*L*-serine Methyl Ester* (**6**): To a solution of *N*-methyl-L-serine methyl ester hydrochloride **5** (4.51 g, 26.6 mmol) in MeOH (90 ml) was added with stirring at 0°C 1 M aqueous NaOH (27 ml) until the pH value reached 8.5−9. Di-*tert*-butyl dicarbonate (6.50 g, 30.2 mmol) was then added within 5 min, and the resulting solution was stirred overnight at room temp. and pH 8−9. Methanol was evaporated in vacuo in a rotatory evaporator with a bath temperature not exceeding 40°C, the residue taken up in saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×50 ml). The combined organic solutions were washed with cold 1 M aqueous HCl, water, brine, dried over $MgSO_4$, filtered and evaporated to give 5.67 g (91%) of **6** as a colorless oil which contained no impurities detectable by NMR spectroscopy and was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, two amide rotamers in the ratio of 1:1): δ = 1.18 and 1.24 (s, 9 H, *t*Bu), 2.70 and 2.75 (s, 3 H, CH_3N), 3.52 (s, 3 H, CH_3O), 3.5−3.7 (m, 2 H), 3.80 (m, 1 H), 4.07 and 4.40 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 27.65 (+, 3 CH_3), 32.27 and 33.15 (+, CH_3N), 51.47 (+, CH_3O), 59.90 and 60.17 (−, CH_2O), 60.45 and 61.85 (+, CH), 79.77 and 80.03 (C_{quat}), 154.76 and 155.93 (C_{quat}, Boc-CO), 170.17 and 170.40 (C_{quat}, $COOCH_3$). − R_f = 0.5 ($CHCl_3$/EtOAc 5:3). An analytical sample was purified by chromatography on silica gel eluting with $CHCl_3$/EtOAc (5:3) as eluent to give **5** as an oil. − $C_{10}H_{19}NO_5$ (233.3): calcd. C 51.49, H 8.21, N 6.00; found C 51.05, H 8.00, N 5.93.

*N-tert-Butoxycarbonyl-N-methyl-O-tosyl-*L*-serine Methyl Ester* (**7**): To a solution of *N-tert*-butoxycarbonyl-*N*-methyl-L-serine methyl ester **6** (312 mg, 1.35 mmol) in anhydrous CH_2Cl_2 (1.5 ml) was added anhydrous pyridine (1 ml) followed by 4-pyrrolidinopyridine (20 mg, 0.135 mmol). Then tosyl chloride (282 mg, 1.48 mmol) dissolved in anhydrous CH_2Cl_2 (1 ml) was added dropwise at 0°C. The reaction mixture was left at 0−5°C overnight, diluted with dichloromethane (10 ml) and poured into crushed ice. Hydrochloric acid (6 M) was added dropwise with shaking until the pH of the aqueous layer reached 2, the organic phase was separated, and the aqueous solution was extracted with CH_2Cl_2 (2×15 ml). The combined organic solutions were washed with water (10 ml), saturated aqueous $NaHCO_3$ solution (2×10 ml), brine, and dried ($MgSO_4$). Evaporation of the solvent in vacuo (bath temperature did not exceed 30°C) gave 450 mg (94%) of **7** as a light-brown oil which was stored at 0−5°C. − R_f = 0.50 (CH_2Cl_2). The product decomposes on silica gel during column chromatography and by heating up to ca. 80°C. − ^{1}H NMR ($CDCl_3$, two amide rotamers in the ratio of 1:1): δ = 1.32 and 1.43 (s, 9 H, *t*Bu), 2.43 (s, 3 H, CH_3Ar), 2.78 and 2.83 (s, 3 H, CH_3N), 3.67 and 3.71 (s, 3 H, CH_3O), 4.31 (m, 1 H) 4.40 − 4.58 (m, 2 H), 7.35 (d, 2 H, *J* = 9 Hz), 7.78 (d, 2 H, *J* = 9 Hz). − ^{13}C NMR ($CDCl_3$): δ = 21.61 (+, CH_3 in Ts), 28.04 and 28.15 (+, 3 CH_3), 34.63 and 35.01 (+, CH_3N), 52.40 (+, CH_3O), 59.39 and 60.24 (+, CH), 67.64 (−, CH_2OTs), 80.71 and 81.10 (C_{quat}), 127.93 and 129.90 (+, C^{ar}), 132.37 (Me-C_{quat}), 145.03 and 145.15 (O_3S-C_{quat}), 156.00 (C_{quat}, Boc-CO), 168.65 (C_{quat}, $COOCH_3$).

*Reaction of N-tert-Butyloxycarbonyl-N-methyl-O-tosyl-*L*-serine Methyl Ester with N-Carbamoylguanidine:* To a solution of *N*-carbamoylguanidine hydrochloride[16] (162 mg, 1.17 mmol) in anhydrous MeOH (3 ml) was added dropwise at 0°C a freshly prepared solution of MeONa [from sodium (27 mg, 1.17 mmol) in MeOH (1 ml)]. The resulting solution was stirred for 30 min at 0°C, and then compound **7** (415 mg, 1.17 mmol), dissolved in anhydrous MeOH (3 ml) was added dropwise. The reaction mixture was stirred for 2 h at 0°C, and was then allowed to warm up to room temp. The progress of the reaction was monitored by NMR spectroscopy (after evaporation of the solvent from a small aliquot of the reaction mixture). After 16 h at room temp. the following compounds were detected: the starting material **7** and *N-tert*-butoxycarbonyl-*N*-methyldehydroalanine methyl ester (**8**) (ratio 1:2) as well as *N*-carbamoylguanidinium tosylate. Compound **8** was identified by comparison of its NMR spectra with those of an authentic sample prepared as described previously[7].

N-tert-Butoxycarbonyl-N-methyldehydroalanine Methyl Ester (**8**): ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 9 H, *t*Bu), 3.05 (s, 3 H, CH_3N), 3.73 (s, 3 H, CH_3O), 5.29 (s, 1 H, $=CH_2$) 5.61 (s, 1 H, $=CH_2$). − ^{13}C-NMR ($CDCl_3$): δ = 27.85 (+, 3 CH_3), 36.40 (+, CH_3N), 51.95 (+, CH_3O), 80.84 (C_{quat}), 115.03 (−, $=CH_2$), 141.31 (C_{quat}, =C<), 153.65 (C_{quat}, Boc-CO), 165.13 (C_{quat}, $COOCH_3$). Addition of triethylamine to the reaction mixture (152 mg, 1.5 mmol) speeded up the reaction but did not change its course.

3,7-Bis(N-tert-butoxycarbonyl-N-methylamino)-3,4,6,7,8,9-hexahydro-2H-pyrimidino[1,2-a]pyrimidine-2,8-dione (**10**): Sodium (299 mg, 13 mmol) was dissolved in anhydrous 2-propanol (30 ml) kept under argon under reflux. After cooling down to room temp., guanidine hydrochloride (1.05 g, 11 mmol) was added, and the resulting mixture was stirred under reflux for 1.5 h. The suspension was cooled to ambient temperature, and the solution of guanidine was filtered directly into a round-bottom flask in the absence of air and moisture. Compound **8** (2.15 g, 10 mmol) in 2-propanol (10 ml) was added over a period of 2 h, and the resulting solution was stirred at room temp. for 48 h. The mixture was preadsorbed on silica gel (10 g) and chromatographed on 150 g of SiO_2 (column 30×4 cm, CH_2Cl_2/MeOH, 15:1) to give 1.92 g (90%) of **10** as a mixture of two isomers, m. p. 135−137°C (C_6H_6, dec.), R_f = 0.37. − ^{1}H NMR ([D_6]DMSO): δ = 1.35 (s, 9 H, *t*Bu), 2.69 (s, 3 H, CH_3N), 3.15−3.35 (m, 1 H), 3.35−3.70 (m, 1 H), 4.40 − 4.70 (m, 1 H), 7.35 (br. s, 1 H). − ^{13}C NMR ([D_6]DMSO, two isomers): δ = 27.90 (+, 3 CH_3), 32.50 and 33.20 (+, CH_3N), 47.14 and 47.76 (−, CH_2), 53.23 and 54.72 (+, CH), 79.51 (C_{quat}), 154.50 and 154.97 (C_{quat}, Boc-CO), 156.56 (C_{quat}, CO), 170.44 (C_{quat}, CO). − MS (EI); *m/z* (%): 425(3) [M^+], 397(3) [M^+ − CO], 352(11) [M^+ − *t*BuO], 296(19) [M^+ − CO − CO_2*t*Bu], 239(8), 213(22), 157(35), 101(40), 57 (100). − MS (HR-EI): 425.2274 ($C_{19}H_{31}N_5O_6$: calcd. 425.2274). − $C_{19}H_{31}N_5O_6$ (425.49): calcd. C 53.63, H 7.34; found C 53.14, H 7.62.

*Reaction of N-tert-Butoxycarbonyl-N-methyl-*L*-serine Methyl Ester* (**6**) *with* HN_3 *According to the Mitsunobu Protocol*[17]: To a solution of triphenylphosphine (1.93 g, 7.37 mmol) in 10 ml THF kept at −78°C under nitrogen were added with stirring one after the other: DEAD (1.25 g, 7.19 mmol) in THF (5 ml), 0.79 M HN_3 (9.0 ml, 7.11 mmol) in benzene (freshly prepared from sodium azide and concentrated sulfuric acid in benzene according to the standard protocol) and ester **6** (1.37 g, 6.14 mmol). The mixture was allowed to warm up to room temp. and was stirred for another 20 h. The TLC of the solution showed only a single spot with the expected R_f = 0.46 (diethyl ether/hexane, 1:1). The solvents were evaporated in vacuo keeping the bath temperature below 40°C, and the residue was chromatographed on silica gel (70 g, column 40×3 cm) eluting with diethyl ether/hexane (0→1:1). The fractions which displayed the same spot as the expected product gave 1.29 g of an oily substance which, according to its NMR spectra was a mixture of compounds **8** and **11** in a ratio of 3:2. No changes were observed when a 1.5-fold excess of HN_3 was used in a second experiment.

β-Azido-N-tert-butoxycarbonyl-N-methyl-L-alanine Methyl Ester (**11**): ^{1}H NMR ($CDCl_3$, two amide-rotamers in a ratio of 1:1): δ = 1.48 and 1.52 (s, 9 H, *t*Bu), 2.86 and 2.90 (s, 3 H, CH_3N), 3.6−3.8 (m, 2 H), 3.73 (s, 3 H, CH_3O), 4.19 and 4.50 (dd, *J* = 5.3 and 9.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 28.01 (+, 3 C), 33.51 and 34.12 (+, CH_3N), 49.50 and 50.12 (−, CH_2N_3), 52.20 (+, CH_3O), 59.32 and 60.42 (+, CH), 80.55 (C_{quat}), 154.36 and 154.51 (C_{quat}, Boc-CO), 165.48 and 165.15 (C_{quat}, $COOCH_3$).

$N^α$-Benzyloxycarbonyl-$N^α$-methyl-DL-asparagine (**14**): Benzyl chloroformate (10.3 ml, 72.1 mmol) was added to a solution of $N^α$-methyl-DL-asparagine (**13**) (10.1 g, 68.8 mmol) in 140 ml of half-concentrated aqueous $NaHCO_3$, then a solution of NaOH (3.0 g, 75 mmol) in water (40 ml) was added dropwise under constant stirring at room temp. within 3 h. Stirring was continued for another 40 min, while additional portions of 2 M aqueous NaOH were added to keep the pH in the range 8−9. The nearly transparent solution was washed with CH_2Cl_2 (2×50 ml) and then carefully acidified with 4 M aqueous HCl. After having kept the reaction mixture in an ice-bath for 1 h, the precipitate was collected on a filter, washed with ice-water and air-dried to give 17.0 g (88%) of **14** as a colorless solid, m. p. 160−162°C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.50−3.10 (m, 2 H, CH_2N), 2.80 and 2.85 (s, 3 H, CH_3N), 4.71−4.89 (m, 1 H, CHCO), 5.06 (br. s, 2 H, CH_2O), 6.93 and 6.97 (br. s, 1 H, NH), 7.26−7.40 (m, 5 H), 7.48 and 7.50 (br. s, 1 H, NH). Two amide rotamers in a ratio of ca. 1:1 at ambient temperature. − ^{13}C NMR ([D$_6$]DMSO): δ = 32.67 and 32.78 (+, CH_3N), 35.16 and 35.64 (−, CH_2CO), 56.49 and 57.05 (+, CHN), 66.44 and 66.58 (−, CH_2O), 127.17 and 127.52 (+, 2 C), 127.78 and 127.97 (+), 128.46 and 128.58 (+, 2 C), 136.94 (C_{quat}), 155.60 and 155.72 (C_{quat}, NHCOO), 171.41 and 171.56 (C_{quat}), 172.26 and 172.36 (C_{quat}). − MS (EI); *m*/*z* (%): 280 (2) [M$^+$], 263 (8) [M −OH$^+$], 91 (100) [$C_7H_7^+$]. − MS (HR-EI): 280.1059 ($C_{13}H_{16}N_2O_5$: calcd. 280.1059).

3-Amino-2-(N-benzyloxycarbonyl-N-methylamino)propionic Acid (**15**): Iodobenzene bis(trifluoroacetate) (22.8 g, 53.0 mmol) and $N^α$-benzyloxycarbonyl-$N^α$-methyl-DL-asparagine (**14**) (10.3 g, 36.6 mmol) were suspended by stirring in 50% (v/v) aqueous DMF (300 ml). After 15 min, pyridine (6.0 ml, 74 mmol) was added, and the mixture was stirred for another 5 h. The emulsion formed was evaporated at 50−70°C under reduced pressure (1−2 Torr) as quickly as possible. The oily residue was taken up in water (180 ml) and washed with ether (4×50 ml). The aqueous layer was once more concentrated in vacuo, and the residue was dissolved in ethanol (30 ml). The pH value was adjusted to 7 with 15 M aqueous ammonia, and the product was carefully precipitated with 400 ml of ether. After stirring in an ice bath for 2 h, the precipitate was filtered off and washed with ether to give, after drying, 6.84 g (74%) of the amino acid **15** with m.p. 200−202°C (dec.); no m. p. was reported[17] for the L-isomer of this acid. − ^{1}H NMR (D_2O): δ = 2.73 (s, 3 H, CH_3N), 3.03−3.14 (m, 1 H), 3.24−3.34 (m, 1 H), 4.24 (dd, *J* = 9.0 and 6.7 Hz, 0.5 H), 4.36 (dd, *J* = 9.0 and 6.7 Hz, 0.5 H), 4.68 (br. s, 3 H), 4.96 and 4.98 (s, 2 H, CH_2O), 7.23−7.33 (m, 5 H). Two amide rotamers in a ratio of ca. 1:1. − ^{13}C NMR (D_2O): δ = 31.10 and 32.36 (+, CH_3N), 37.53 and 37.84 (−, CH_2N), 58.09 and 58.60 (+, CHN), 66.78 and 66.91 (−, CH_2O), 126.75 and 126.86 (+, 2 C), 127.27 (+), 127.55 (+, 2 C), 134.64 and 134.83 (C_{quat}), 156.35 and 156.91 (C_{quat}, NHCOO), 172.72 and 172.77 (C_{quat}, COOH). − MS (EI); *m*/*z* (%): 252 (0.2) [M$^+$], 223 (37) [M − CH_2NH^+], 148 (20), 132 (18), 91 (100) [$C_7H_7^+$]. − MS (CI, NH_3); *m*/*z* (%): 270 (20) [M + NH_4^+], 253 (71) [M + H$^+$], 211 (100), 183 (74), 106 (33).

3-Amino-2-(N-benzyloxycarbonyl-N-methylamino)propionic Acid Methyl Ester Hydrochloride (**16**): To a solution of thionyl chloride (11.6 ml, 162 mmol) in anhydrous MeOH (135 ml) at −20 to −10°C was added with stirring after 10 min the amino acid **15** (11.2 g, 44.4 mmol). The resulting thick suspension was stirred at room temp. for 24 h to give a clear solution which was concentrated in vacuo. The residue was dissolved in methanol (150 ml), and the solution concentrated once more. The solid residue was crystallized from a MeOH−ether mixture at −20°C to give 13.1 g (98%) of **16** as a snow-white solid, m. p. 175−176°C. The NMR spectra disclosed the presence of two amide rotamers (ca. 2:1). − Major isomer (common signals are marked with *), ^{1}H NMR ([D$_6$]DMSO): δ = 2.95 (s, CH_3N), 3.19−3.30* (m, 2 H), 3.63 (s, CH_3O), 4.74−4.82* (m, 1 H), 5.06 and 5.11 (AB, J = 12.8 Hz, CH_2O), 7.27−7.43* (m, 5 H), 8.55* (br. s, 3 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 34.63 (+, CH_3N), 37.48 (−, CH_2N), 52.11* (+, CH_3O), 58.72 (+, CHN), 66.72 (−, CH_2O), 127.46* (+), 127.77* (+), 127.91* (+), 127.99* (+), 128.44* (+), 136.57 (C_{quat}), 155.97 (C_{quat}, NHCOO), 168.99 (C_{quat}, $COOCH_3$). − Minor isomer, ^{1}H NMR ([D$_6$]DMSO): δ = 2.93 (s, CH_3N), 3.52 (s, CH_3O), 5.02 and 5.06 (AB, *J* = 12.8 Hz, CH_2O). − ^{13}C NMR ([D$_6$]DMSO): δ = 35.34 (+, CH_3N), 38.20 (−, CH_2N), 58.29 (+, CHN), 66.88 (−, CH_2O), 136.25 (C_{quat}), 155.18 (C_{quat}, NHCOO), 169.08 (C_{quat}, $COOCH_3$). − MS (EI); *m*/*z* (%): 267 (1) [M$^+$], 237 (80) [M − CH_2NH^+], 162 (24), 146 (42), 102 (50), 91 (100) [$C_7H_7^+$]. − MS (FAB); *m*/*z* (%): 267 (100) [M$^+$]. − $C_{13}H_{18}N_2O_4$*HCl (302.76): calcd. C 51.57, H 6.33, N 9.25; found 51.23, H 6.24, N 9.23.

2-Methyl-2-thiopseudobiuret Hydroiodide (**18**) was synthesized according to the published procedure[12][13]. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.67 (s, CH_3S), 6.70 (br. s, 1 H), 7.72 (br. s, 1 H), 10.65 (br. s, 3 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 13.62 (+), 153.34 (C_{quat}), 171.45 (C_{quat}).

5-(N-Benzyloxycarbonyl-N-methylamino)-3,4,5,6-tetrahydro-2-ureidopyrimidin-4-one (**3-Z**): A suspension of the amino ester hydrochloride **16** (24.0 g, 79.2 mmol), isothiuronium salt **18** (20.7 g, 79.2 mmol) and NaOAc (14.5 g, 176 mmol) in 600 ml of 2-propanol was refluxed with stirring under nitrogen for 24 h. After cooling, the precipitate was collected on a filter, washed with 2-propanol and ether, and shaken with 3% aqueous $NaHCO_3$ (50 ml) for 10 min. The solid precipitate was filtered off with suction, washed with water (20 ml), MeOH (20 ml), and ether to give 8.92 g (35%) of **3-Z** as a poorly soluble colorless solid, m. p. 210−212°C. − ^{1}H NMR ([D$_6$]DMSO, ambient temp.): δ = 2.83 and 2.85 (s, 3 H, CH_3N), 3.50−3.75 (m, 2 H, CH_2N), 4.60−4.80 (m, 1 H, CHN), 5.04 and 5.10 (s, 2 H, CH_2O), 6.96 (br. s, 1 H, NH), 7.23−7.50 (m, 5 H), 7.52 (br. s, 1 H, NH), 9.75 (br. s, 2 H, NH). Two amide rotamers (ca. 2:1). − ^{13}C NMR ([D$_6$]DMSO, 50°C): δ = 32.15 (+, CH_3N), 54.12 (+, br., CHN), 66.34 (−, CH_2O), 127.20 (+, 2 C), 127.56 (+), 128.14 (+, 2 C), 136.53 (C_{quat}), 155.59 (C_{quat}), 156.64 (C_{quat}, br.), 158.04 (C_{quat}), 172.64 (C_{quat}, br.), the signal of CH_2N carbon overlapped with a signal of the solvent. − MS (EI); *m*/*z* (%): 319 (5) [M$^+$], 276 (3) [M − $HNCO^+$], 155 (37), 154 (21), 111 (21), 91 (100) [$C_7H_7^+$]. − MS (HR-EI): 319.1280 ($C_{14}H_{17}N_5O_4$: calcd. 319.1281).

2-(N-Benzyloxycarbonyl-N-methylamino)-3-(3-carbamoylguanidino)propionic Acid (**19**): A suspension of the amino acid **15** (505 mg, 2.00 mmol) and the isothiuronium salt **18** (1.044 g, 4.00 mmol) in water (5 ml) was treated under stirring with 2 N aqueous NaOH until pH 11 was reached, and the clear solution was stirred at room temp. for 19 h. The precipitated product was collected on a filter with suction, washed with hot water (10 ml), ethanol (10 ml), and ether, and dried. Yield 482 mg (71%) of **19** as a colorless solid, m. p. 225−230°C. − ^{1}H NMR ([D$_6$]DMSO, ambient temp.): δ = 2.82 (s, 3 H, CH_3N), 3.45−3.75 (m, 2 H, CH_2N), 4.05 and 4.20 (m, 1 H, CHN), 5.03 and 5.09 (s, 2 H, CH_2O), 7.08 (br. s, 1 H, NH), 7.23−7.45 (m, 5 H), 8.05 (br. s, 1 H, NH), 8.67 (br. s, 1 H, NH), 9.08 (br. s, 1 H, NH), 9.32 (br. s, 1 H, NH), 13.25 and 13.30 (br. s, 1 H, NH). Two amide rotamers (ca. 1:1). − ^{1}H NMR ([D$_6$]DMSO, 100°C): δ = 2.85 (s, 3 H, CH_3N), 3.59 (d, *J* = 7 Hz, 2 H, CH_2N), 4.13 (t, *J* = 7 Hz, 1 H, CHN), 5.08 and 5.09 (AB, *J* = 13 Hz, 2 H, CH_2O), 7.23−7.40 (m, 5 H). − ^{13}C NMR (D_2O+NaOH, ambient temp.): δ = 31.43 and 31.82 (+, CH_3N), 39.58 (−, br., CH_2N), 60.50 (+, br., CHN), 67.39 and 67.67 (−, CH_2O), 127.25 (+), 127.40 (+), 127.56 (+), 128.06 (+), 128.48 (+), 135.86 and 136.21 (C_{quat}), 157.56 and 157.82 (C_{quat}, NHCOO), 160.33 and 160.46 (C_{quat}, br.), 167.29 (C_{quat}, br.), 175.42 (C_{quat}, br.) − $C_{14}H_{19}N_5O_5$ (337.34): calcd. C 49.85, H 5.68, N 20.76; found C 49.80, H 5.32, N 20.30.

Reaction of 2-(N-Benzyloxycarbonyl-N-methylamino)-3-(3-carbamoylguanidino)propionic Acid (**19**) *with 1-(3-dimethylanimopropyl)-3-ethylcarbodiimide Hydrochloride:* A suspension of the acid **19** (169 mg, 0.50 mmol), the carbodiimide (100 mg, 0.52 mmol) and 4-pyrrolidinopyridine (5 mg, 0.03 mmol) in DMF (20 ml) was stirred at room temp. for 3 d. The solvent was evaporated at 30−50°C under reduced pressure (1 Torr), and the residue was treated with diluted $NaHCO_3$ solution (5 ml), the solids were filtered off, washed with water (5 ml), ethanol (5 ml) and ether, and dried in the air. According to the NMR spectra, the solid residue (50 mg) consisted of the acid **19** and the cyclization product **3-Z** (ca. 1:1).

3,4,5,6-Tetrahydro-5-methylamino-2-ureidopyrimidin-4-one (**3**): To a solution of 5-(*N*-benzyloxycarbonyl-*N*-methylamino)-3,4,5,6-tetrahydro-2-ureidopyrimidin-4-one (**3-Z**) (4.00 g, 12.5 mmol) in dimethylacetamide (100 ml) kept under N_2 was added with stirring at room temp. 10% Pd/C (500 mg). The reaction mixture was purged with H_2 for 15 min, and stirring was continued overnight in a slow flow of hydrogen. The mixture was purged with N_2, filtered through a 1 cm layer of Celite®, the solvent evaporated at 30−50°C under reduced pressure (1 Torr), and the residue was stirred with ether (100 ml). The solid was filtered off with suction, washed with ether, and dried in the air to give 2.31 g (100%) of **3** as a colorless solid, m. p. 186−188°C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.30 (s, 3 H, CH_3N), 3.08−3.20 (m, 2 H, CH_2N), 3.66 (m_c, 1 H, CHN), 7.00 (br. s, 1 H, NH), 8.02 (br. s, 1 H, NH), 9.8 (br. s, 2 H, NH). − ^{13}C NMR ([D$_6$]DMSO): δ = 34.33 (+, CH_3N), 41.82 (−, CH_2N), 56.02 (+, CHN), 157.85 (C_{quat}, br.), 158.11 (C_{quat}), 178.10 (C_{quat}, br.). − MS (EI); *m/z* (%): 185 (63) [M^+], 168 (52) [$M - NH_3^+$], 156 (29), [$M - CH_2NH^+$], 142 (9) [$M - HNCO^+$], 129 (28), 115 (42), 86 (30), 72 (25), 71 (28), 57 (100), 43 (48). − MS (HR-EI): 185.0912 ($C_6H_{11}N_5O_2$: calcd. 185.0913).

N^α,N^δ,N^ω-Tri(benzyloxycarbonyl)-L-arginine (**20b**) was prepared according to the reported procedure[18] in 71% yield and recrystallized from hexane/CH_2Cl_2 (1:1, v/v). Its melting point, optical rotation, and ^{1}H-NMR spectrum were identical with the reported data. − ^{13}C NMR ([D$_6$]DMSO): δ = 25.37 (−), 28.11 (−), 44.20 (−), 53.80 (+), 65.45 (−), 66.15 (−), 68.25 (−), 127.78 (+), 127.87 (+), 128.00 (+), 128.39 (+), 128.57 (+), 135.32 (C_{quat}), 137.00 (C_{quat}), 137.14 (C_{quat}), 154.99 (C_{quat}), 156.21 (C_{quat}), 159.75 (C_{quat}), 162.94 (C_{quat}), 173.84 (C_{quat}).

(*S*)*-1,3-Di(benzyloxycarbonyl)-1-(4-benzyloxycarbonyamino-6-diazo-5-oxohexyl)guanidine* (**21b**): Triethylamine (3.0 ml, 22 mmol) and isobutyl chloroformate (2.8 ml, 22 mmol) were added with stirring to a cooled (−20°C) solution of **20b** (12.2 g, 21.0 mmol) in CH_2Cl_2 (240 ml), and the mixture was stirred for an additional 15 min. An etheral solution of diazomethane (60 ml, prepared from 6.2 g of crude *N*-methyl-*N*-nitrosourea) was added to the mixed anhydride thus prepared, and the resulting solution was kept at −5 to 0°C for 22 h. The mixture was washed with half-saturated $NaHCO_3$ solution, water, and brine. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to dryness. Crystallization of the residue from CH_2Cl_2−ether gave 10.7 g (84%) of **21b** as light yellow crystals, m. p. 116−118°C,[19] $[α]_D^{20}$ −13.0° (*c* = 1.2, acetone), but 0.0° (!) (*c* = 1.0, $CHCl_3$). − IR (KBr): ṽ = 3384 cm^{-1}, 3307, 2957, 2111 (CN_2), 1721, 1688, 1610, 1507, 1382, 1258, 1196, 1101, 1003, 752, 697. − ^{1}H NMR: δ = 1.62−1.90 (m, 4 H), 3.88−4.06 (m, 2 H), 4.24−4.40 (m, 1 H), 4.96−5.26 (m, 4 H), 5.26 (s, 2 H), 5.46 (br. s, 1 H, CHN_2), 6.30 (br. d, 1 H), 7.25−7.50 (m, 15 H), 9.34 (br. s, 1 H), 9.53 (br. s, 1 H). − ^{13}C NMR: δ = 24.57 (−), 28.06 (−), 44.16 (−), 54.04 (+), 57.57 (+, CHN_2), 66.74 (−), 66.92 (−), 68.88 (−), 127.96 (+), 128.06 (+), 128.20 (+), 128.43 (+), 128.71 (+), 128.78 (+), 134.43 (C_{quat}), 136.27 (C_{quat}), 136.37 (C_{quat}), 155.60 (C_{quat}), 155.99 (C_{quat}), 160.60 (C_{quat}), 163.46 (C_{quat}), 193.92 (C_{quat}). − MS (EI); *m/z* (%): 572 (1) [$M - N_2^+$], 108 (67), 91 (100) [$C_7H_7^+$]. − MS (CI, NH_3); *m/z* (%): 601 (49) [$M + H^+$], 573 (100) [$M - N_2 + H^+$]. − MS (HR-EI): 572.2270 ($C_{31}H_{32}N_4O_7$: calcd. 572.2271 for $M - N_2^+$).

5-{N-Methyl-N-[N^β,N^ε,N^ω-tri(benzyloxycarbonyl)-(S)-β-homoarginyl]amino}-3,4,5,6-tetrahydro-2-ureidopyrimidin-4-one (**23**): A solution of **21b** (4.41 g, 7.34 mmol) and **3** (1.47 g, 7.94 mmol) in DMA (250 ml, HPLC grade, Aldrich) was irradiated in a pyrex reactor with a medium pressure mercury lamp (150 W) under nitrogen at room temp. for 3 h. The solvent was evaporated at 30−50°C under reduced pressure (1 Torr), the residue was dissolved in warm CH_2Cl_2 (150 ml), the solution washed quickly with water (2×50 ml), brine (50 ml), dried over a small portion of $MgSO_4$, the solvent evaporated, and the residue crystallized from ether−CH_2Cl_2 to give 2.07 g of crude **23**, m. p. 110−117°C. Further recrystallization from CH_2Cl_2 gave 1.67 g (30%) of pure **23**, m. p. 126−131°C. − ^{1}H NMR: δ = 1.50−1.80 (m, 4 H, γ+δ-H), 2.43−2.60 (m, 2 H, α-H), 2.83 and 2.88 (s, 3 H, CH_3N), 3.30−3.62 (m, 2 H, 6-H), 3.87−4.10 (m, 3 H, β+ε-H), 4.85 and 5.0 (m, 1 H, 5-H), 5.07 (m, 2 H, β-$PhCH_2$), 5.12 (s, 2 H, $PhCH_2$), 5.24 (s, 2 H, $PhCH_2$), 5.77 and 5.93 (d, 1 H, β-NH), 7.23−7.45 (m, 15 H, Ph), 9.28 (br. s, 2 H), 9.45 (br. s, 1 H), 10.25 (br. s, 1 H), 11.6 (br, 1 H). − The product was a mixture of diastereomers in a ratio of ca. 1:1. A sample with diastereomeric ratio 3:1 was obtained after another recrystallization from $CHCl_3$ accompanied with a great loss of the substance. − ^{1}H NMR ([D$_6$]DMSO, 50°C): δ = 1.30−1.82 (m, 4 H, γ+δ-H), 2.30−2.60 (m, 2 H, α-H), 2.63 and 2.86 (major) (s, 3 H, CH_3N), 3.20−3.60 (m, 2 H, 6-H), 3.80−3.90 (m, 3 H, β+ε-H), 4.93 (m, 1 H, 5-H), 4.98 (m, 2 H, β-$PhCH_2$), 5.06 (s, 2 H, $PhCH_2$), 5.12 (s, 2 H, $PhCH_2$), 6.60 (br., 2 H), 7.00 (br. s, 1 H), 7.22−7.42 (m, 15 H, Ph), 9.09 (br. s, 2 H), 9.3 (br, 1 H). − ^{13}C NMR ([D$_6$]DMSO, 50°C): δ = 25.00, 31.11 (br), 32.82, 38.10 (br), 44.47, 47.75 (br), 47.96 (br), 52.16, 64.94, 65.98, 67.96, 127.32, 127.40, 127.51, 127.64, 128.00, 128.04, 128.27, 135.10, 136.96 (2 C), 154.76, 155.26 (br), 159.0 (br), 159.44, 162.66, 170.62 (br), 170.72 (br). − MS (FAB); *m/z* (%): 758 (100) [$M + H^+$], 759 (35) [$M + 2 H^+$], 780 (45) [$M + Na^+$].

3,4,5,6-Tetrahydro-5-{N-methyl-N-[(S)-β-homoarginyl]amino}-2-ureidopyrimidin-4-one Dihydrochloride, TAN-1057 A/B (**1a/b**). To a suspension of the tris-Z-derivative **23** (1.16 g, 15.3 mmol of the 1:1 epimeric mixture) in anhydrous MeOH (100 ml) was added $PdCl_2$ (28.7 mmol). The reaction vessel was degassed, charged in three cycles with H_2 and stirred for 2 h under a slow flow of H_2. The suspension was purged with N_2, the catalyst filtered off, and the filtrate evaporated in vacuo to dryness. The solid residue was suspended in anhydrous diethyl ether (100 ml), quickly filtered off, washed with ether 2 × 20 ml) and died in vacuo to give 670 mg (102%) of **1a/1b** as a colorless, slightly hygroscopic solid. The sample contained about 4% (by weight) of methanol according to its ^{1}H NMR (D_2O) spectrum which corresponded to the data reported in the original publications[1][4]. ^{13}C NMR (D_2O): $\delta = 27.00$ (−, C-5′, reference signal), 32.09 (−, C-4′), 37.01 and 37.22 (+, CH_3-N in **1a**, **b**), 37.79 and 37.74 (−, C-2′), 41.40 and 41.45 (−, C-6 in **1a**, **b**), 43.44 (−, C-6′), 51.19 (+, C-3′), 56.46 and 56.68 (+, C-5 in **1a**, **b**), 159.68 (C_{quat}, guanidino), 160.32 (br., C_{quat}, C-2), 161.53 (br., C_{quat}, ureido), 175.27 and 175.32 (C_{quat}, C-1′ in **1a**, **b**), 178.07 (br., C_{quat}, C-4).

☆ Dedicated to Professor *Lars Skattebøl* on the occasion of his 70th birthday.

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